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(71) Applicant *(for all designated States except US)*: **YALE UNIVERSITY** [US/US]; 451 College Street, New Haven, CT 06520 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **CHENG, Yung-Chi** [US/US]; 961 Baldwin Road, Woodbridge, CT 06525 (US). **LIU, Shwu-Huey** [US/US]; 92 Joshua Trail, Madison, CT 06443 (US).

(74) Agent: **MORGAN LEWIS & BOCKIUS LLP**; Sally P. Teng, 1800 M Street, N.W., Washington, DC 20036-5869 (US).

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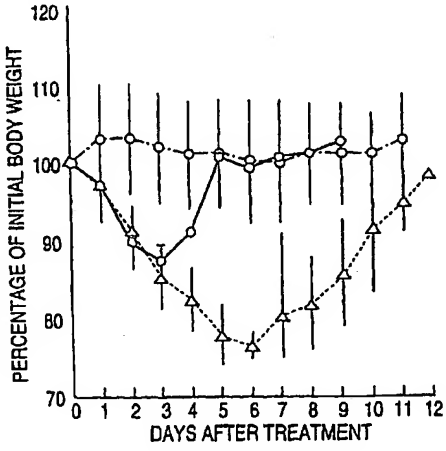
(54) **Title:** HERBAL COMPOSITION PHY906 AND ITS USE IN CHEMOTHERAPHY



N = 4	NO TREATMENT (DAY 3)	CPT-11 300 mg/kg (DAY 3)	CPT-11 400 mg/kg (DAY 6)
NO TREATMENT (DAY 3)	——	P < 0.01	P < 0.01
CPT-11 300 mg/kg (DAY 3)	P < 0.01	——	P < 0.05
CPT-11 400 mg/kg (DAY 6)	P < 0.01	P < 0.05	——

(57) **Abstract:** This invention provides herbal compositions useful for increasing the therapeutic index of drugs, including those used in the treatment of disease, especially viral infections and neoplasms of cancer. This invention provides methods useful for improving the quality of life of an individual undergoing chemotherapy. Furthermore, this invention improves the treatment of disease by increasing the therapeutic index of chemotherapy drugs by administering the herbal composition PHY906 to a person undergoing such chemotherapy.

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HERBAL COMPOSITION PHY906 AND ITS USE IN CHEMOTHERAPY

Yung-Chi Cheng and Shwu-Huey Liu

FIELD OF THE INVENTION

The present invention relates to herbal compositions and herbal extracts useful for increasing the therapeutic index of drugs, including those used in the treatment of disease, especially viral infections and neoplasms of cancer. The methods of the present invention can be used to improve the quality of life of an individual undergoing chemotherapy. Specifically, the invention relates to the treatment of disease by increasing the therapeutic index of chemotherapy drugs by the herbal composition PHY906. More specifically, the invention relates to the treatment of cancer by increasing the therapeutic index of cancer chemotherapy drugs by the herbal composition PHY906.

BACKGROUND OF THE INVENTION

All publications and patent applications herein are incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

I. Herbal Medicine

Herbal medicine has been in use for centuries by people of Asia and Europe. In the United States (US), herbs have become commercially valuable in the dietary supplement industry as well as in holistic medicine. Approximately one third of the US population has tried some form of alternative medicine at least once (Eisenberg *et al.*, N. Engl. J. Med., 328:246-252 (1993)). Botanicals have also become a focal point for the identification of new active agents to treat diseases. Active compounds, derived from plant extracts, are of continuing interest to the pharmaceutical industry. For example, taxol an antineoplastic drug obtained from the bark of the western yew tree, has been

found to be useful in the treatment of breast cancer (Gomez-Espuch *et al.*, Bone Marrow Transplant, 25(3):231-235 (2000)).

There are many branches of herbal medicine around the world, such as Ayurveda, Unani, Sida and Traditional Chinese Medicine (TCM). While modern Western medicine typically consists of administering a single chemical entity capable of intervening a specific biochemical pathway, each formula of TCM contains hundreds of chemical entities from several herbs which are designed to interact with multiple targets in the body in a coordinated manner. Although empirical practice contributed in a significant way to the herbal composition and prescription of these ancient herbal medicines, they are also supported, to a varying degree, by a set of theories which all are distinct from that of modern Western medicine in terms of anatomy, pharmacology, pathology, diagnosis treatment, *etc.* Among the different herbal medicine fields, TCM has developed a more complete set of theories over several centuries which have been well documented and practiced by local physicians caring for a huge population (>1.3 billion people) in greater China and in East Asia including Korea and Japan.

II. Traditional Chinese Medicine

Western medicine generally uses purified compounds, either natural or synthetic, mostly directed towards a single physiological target. However, the compositions used in TCM are usually composed of multiple herbs and compounds which are aimed at multiple targets in the body based on unique and holistic concepts. TCM mainly use processed crude natural products, with various combinations and formulations, to treat different conformations resulting in fewer side effects. The great potential of TCM has yet to be realized for the majority of the world's people.

Mixtures of botanical extracts, rather than a single compound are widely used throughout the world for the management of disease and are slowly gaining increased acceptance in Western countries (Okada, F., Lancet 348: 5-6(1996); Xiao PG, Xing ST and Wang LW, Journal of Ethnopharmacol 38: 167-175(1993)). The use of traditional

Chinese medicine is based on the interaction of many chemical components in an herbal preparation that act simultaneously and synergistically on multiple molecular targets and cellular mechanisms. These components serve various functions; some may be responsible for efficacy while others may decrease toxicity or increase bioavailability. Chinese herbal formulations are perhaps the best known botanical drugs and have been derived from empiric observations in humans over the millennia. The claimed indication of a given Chinese medicinal preparation, in many cases, is multiple rather than single. This is not surprising, due to the many phyto-chemical ingredients in a formulation that could exert actions at multiple targets. It is possible that one Chinese medicinal formulation may relieve more than one side effect associated with the use of cancer chemotherapeutic agents.

The herbs in a typical TCM prescription are assigned roles as the principal herb and the secondary herbs, including assistant, adjuvant and guiding herbs. The principal herb produces the leading effects in treating the cause or the main symptom of a disease. An assistant herb helps to strengthen the effect of the principal herb and produces leading effects in the treatment of the accompanying symptoms. There are three types of adjuvant herbs: 1) those that enhance the therapeutic effects of the principal and assistant herbs or treat tertiary symptoms, 2) those that reduce or eliminate the toxicity and other side effects of the principal and the assistant herbs and 3) those that act on complementary target tissues not specifically affected by the principal herb. A guiding herb directs the effect of other herbs to the affected site and/or coordinates and mediates the effects of the other herbs in the prescription or formulation. In contrast to most of the herbal medicines or supplements that consist of one or more parts of a single plant, the intended effects of TCM are directed at multiple tissues.

For example, a well-known TCM recipe, "Ephedra Decoction" used for treating asthma is composed of ephedra, cinnamon twig, bitter apricot kernel and licorice. Ephedra, as the principal herb, which expels cold, induces diaphoresis and facilitates the flow of the Lung Qi to relieve asthma, the main symptom. Cinnamon twig, as the

assistant herb, enhances ephedra's induction of diaphoresis and warms the Channels to ensure the flow of Yang Qi for reducing headache and pantalgia. Bitter apricot kernel, as the adjuvant herb, facilitates the adverse flow of the Lung Qi and strengthens the asthma relief by ephedra. Licorice as the guiding herb moderates the effects of both ephedra and cinnamon to ensure a homeostasis of the vital Qi. While each of the four herbs clearly exhibits its respective activity, they complement as well as supplement each other when they are combined. In practice, the principal herb can be prescribed with one or more secondary herbs, depending on the symptoms at a patient's presentation (Prescriptions of Traditional Chinese Medicine; Chapter One, pp10-16, E. Zhang, editor in Chief, Publishing House, Shanghai University of Traditional Chinese Medicine, 1998).

Qi refers to the total energy of the body. Herbs are used to achieve the optimum balance of Qi; that balance is believed to manifest itself in the overall health and vigor of the patient (K. C. Huang, The Pharmacology of Chinses Herbs, Second Edition, Page 2, 1999, CRC Press).

The main theories of TCM that guide the treatment of sickness with herbal medicine and other means, such as acupuncture, are 1) the theory of Yin and Yang; 2) the theory of Five Elements; 3) the theory of Viscera and Bowels; 4) the theory of Qi, Blood and Body Fluid; and 5) the theory of Channels and Collaterals.

In TCM, the first important aspect of making the proper diagnosis is to ascertain whether the disease is Yin or Yang, the two forces which the Chinese believe control the workings of the universe. Yin represents the feminine side of nature, encompassing darkness, tranquility, depth, cold, and wetness, while Yang represents a masculine principle, encompassing light, activity, height, heat, and dryness (K. C. Huang, The Pharmacology of Chinese Herbs, Second Edition, Page 2, 1999, CRC Press). Yin is commonly interpreted to be a negative force, while yang represents a positive force. The two forces are complementary, and neither can exist without the other. Thus, TCM attempts to achieve a balance between Yin and Yang.

In diagnosing a patient based on the philosophy of Yin and Yang, those patients who have a fever, are thirsty, constipated or have a rapid pulse condition are of Yang character. Those individuals who have an aversion to cold, are not thirsty, and diarrhea and a slow pulse condition are of Yin character. The property, flavor and function of herbs can also be classified according to Yin and Yang theory. For example, herbs of cold and cool nature belong to Yin, while herbs which are warm and hot in nature belong to Yang. Herbs with sour, bitter and salty flavor belong to Yin, while herbs with pungent, sweet and bland flavor belong to Yang. Herbs with astringent and subsiding function belong to Yin, while herbs with dispersing, ascending and floating function belong to Yang. In TCM, the principles of treatment are based on the predominance or weakness of Yin and Yang. Herbs are prescribed according to their property of Yin and Yang and their function for restoring the imbalance of the Yin and Yang. In so doing, the benefit of treatment is achieved.

According to the theory of Five Elements there are five basic substances that constitute the material world (*i.e.*, wood, fire, earth, metal and water). In TCM this theory has been used to explain the physiology and pathology of the human body and to guide clinical diagnosis and treatment. Herbal physicians have applied the laws of generation, restriction, subjugation, and reverse restriction of the five elements to work out many effective and specific treatment regimens, such as reinforcing earth to generate metal (strengthening the function of the spleen to benefit the lung), replenishing water to nourish wood (nourishing the essence of the kidney to benefit the liver), supporting earth to restrict the wood (supplementing the function of the spleen to treat the hyperactivity of the liver), and strengthening water to control fire (replenishing the essence of the kidney to treat hyperactivity of the heart). Specifically, the property of some herbs is assigned to each of the five Elements for the purposes of guiding the prescription of a TCM recipe.

In TCM, the internal organs of the human body are divided into three groups: five Viscera (the Heart, the Liver, the Spleen, the Lung and the Kidney), Six Bowels (the Gall Bladder, the Stomach, the Large Intestine, the Small Intestine, the Urinary Bladder, and

the Triple Warmer), the Extraordinary Organs (the Brain, the Medulla, the Bone, the Blood Vessel, the Gall Bladder, and the Uterus). In TCM, the Viscera or the Bowel are not only anatomic units, but also concepts of physiology and pathology concerning interactions among different organs. For example, the heart also refers to some of the mental functions and influence functions of blood, hair, tongue, and skin. Yin and Yang and the Five Elements influence the interactions among these internal organs, Viscera, Bowels, and Extraordinary Organs. The complexity of interplay of the theories is used to explain the pathology of diseases to which herbs are prescribed, as discussed below.

The prescription of herbal medicine in TCM starts with the diagnosis, which consists of four main items: interrogation, inspection, auscultation and olfaction, pulse taking and palpation. During the interrogation phase, much information is gathered, including the characteristics of the main symptoms. For instance, if the main symptom is characterized by the dull pain of the epigastric region, which may be relieved by warming and pressing, this suggests the insufficiency of the Spleen-Yang. Soreness and weakness of the loins and knees, intolerance of coldness with cold extremities manifests a weakness of the Kidney-Yang. During inspection, observations are made for vitality, skin color, and the general appearance and the condition of the tongue. For example, a pale complexion corresponds internally to the Lung of autumn, whose Qi is dry. This may occur when Yang Qi is lacking and the circulation of Qi and blood is impeded, or when the coldness in the channels and collaterals causes them to contract.

In TCM, it is from Qi, blood, and body fluid that come energy needed by the Viscera and Bowels, Channels and Collaterals, tissues, and other organs for carrying-out their physiological functions; and on which the formation and metabolism of Qi, blood and body fluid depend. Prescriptions of TCM consider the herbal effects on Qi and blood for treatments.

TCM holds that Channels, Collaterals, and their subsidiary parts are distributed over the entire body It is through them that herbs exert influence on pathological targets and achieve the improvement of sickness. For example, ephedra acts on the Channels of

the Lung and Urinary Bladder so as to induce sweat for relieving asthma and promoting diuresis. As noted above, clinical applications of acupuncture are also guided by the theory of Channels and Collaterals.

In summary, while the nature or property of each herb in TCM may be assigned as Yin or Yang, and to one of the Five Elements, they act through Channels and Collaterals and are mediated via Qi, Blood and Fluid to yield therapeutic effects on targets, such as Viscera and Bowels. Pathogenic factors may be disguised as decoys through the very same systems of Channels and Collaterals to adversely affect the functions of Viscera and Bowels and thus cause sickness.

III. The Patenting of Herbal Compositions in the United States

U.S. Patents have been issued for herbal compositions used for the treatment of various diseases and other health-related problems afflicting mammals, including humans. For example, herbal compositions which include *Paeonia suffuticosa* have been found useful for treating viral infections, including infection from herpes and polio virus (U.S. Patent No. 5,411,733).

Ocular inflammation can be treated with a pharmaceutical composition containing the plant alkaloid tetrandrine (U.S. Patent No. 5,627,195). U.S. Patent No. 5,683,697 discloses a pharmaceutical composition having anti-inflammatory, anti-fever, expectorant or anti-tussive action, wherein the composition includes plant parts from the species *Melia, Angepica, Dendrobium, Impatiens, Citrus, Loranthus, Celosia, Cynanchum* and *Glehnia*. An herbal formulation comprising extracts of the roots, rhizomes, and/or vegetation of *Alphinia, Smilax, Tinospora, Tribulus, Withania* and *Zingiber* has been found to reduce or alleviate the symptoms associated with rheumatoid arthritis, osteoarthritis, and reactive arthritis and to reduce the production of proinflammatory cytokines (U.S. Patent No. 5,683,698). Compositions containing talc, silkworm excrement, and the ingredients of twelve different herbs have been shown to be effective in reducing inflammation, pain, and fever in mammals (U.S. Patent No. 5,908,628).

Patents have also been issued for herbal compositions which find use in the treatment of cancer and cancer-related health problems. For example, U.S. Patent No. 5,437,866 discloses a composition comprising a mixture of herbs, including species of *Scutellaria barbata*, as well as their extracts, which is used to ameliorate the effects of malignancy in humans. U.S. Patent No. 5,665,393 discloses various herbal compositions which include *Glycyrrhiza glabra L.* and *Scutellaria baicalensis Georgi*, *Rabdosia rubescens*, and *Serenoa repens* for the treatment of prostate carcinoma. Further, antitumor herbal compositions include *Astragali radix*, *Paeonia radix*, *Cinnamomi cortex*, *Rhemannia radi* and *Glycyrrhizae radix* for use in increasing antitumor activity of mitomycin D and doxorubicin (U.S. Patent No. 4,613,591 and U.S. Patent No. 4,618,495).

IV. Adverse Effects of Cancer Chemotherapy

Medical oncology has had a great impact in changing the practice of medicine in the past several decades, as curative treatments for a variety of previously fatal malignancies have been identified. However, few categories of drugs in common use have a narrower therapeutic index and a greater potential for causing harmful side effects than do the antineoplastic drugs (Calabresi and Chabner, 1996).

Anticancer agents, like many other potent drugs with only moderate selectivity, may cause severe toxicity. Common adverse effects associated with cancer chemotherapy include, but are not limited to, gastrointestinal complications (*e.g.*, diarrhea, nausea, vomiting, anorexia and mucositis), pain, appetite loss, bone marrow/hematological complications (*e.g.*, leukopenia, neutropenia, anemia, hemorrhage, and thrombocytopenia), fatigue and sleep disturbance.

The inventors of the present invention performed a literature search for Chinese medicinal formulations that have been used for the treatment of symptoms associated with cancer chemotherapy. TJ-14, a botanic formulation with seven herbs, was reported to potently prevent diarrhea caused by CPT-11 in cancer patients (Kase, Y, Hayakawa T,

and Aburada M. *et al.*, Jpn. J. Pharmacol. 75, 407-413 (1997); Marita M., Nagai E and Hagiwara H. *et al.*, Xenobiotica. 23, 5-10 (1993)). The diarrhea was proposed to occur from the accumulation of SN-38, an active metabolite of CPT-11, created by intestinal microorganisms. The inventors believe that baicalin, an inhibitor of β-glucuronidase, is the active ingredient in TJ-14 that alleviates diarrhea caused by CPT-11 (Kase, Y, Hayakawa T, and Aburada M. *et al.*, Jpn. J. Pharmacol. 75, 407-413 (1997); Marita M., Nagai E and Hagiwara H. *et al.*, Xenobiotica. 23, 5-10 (1993); Takasuna K, Takehiro H, Hirohashi M, *et al.*, Cancer Chemother Pharmacol. 42:280-286 (1998); Takasuna K, Takehiro H, Hirohashi M, Kato M, *et al.*, Cancer Res. 56:3752-3757 (1996)). Therefore, several Chinese herbal formulations containing the root of *Scuellaria baicalensis Georgi*, which is rich in baicalin, were evaluated. Among several formulations examined in the laboratory, the inventors chose PHY906. This specific formulation was established more than 1500 years ago for the treatment of diarrhea, abdominal spasms, fever, headache, vomiting, nausea, extreme thirst, and subcardial distention (Shang Han Lun of the Han Dynasty; Hong-Yen Hsu and Chau-Shin Hsu, Commonly used Chinese Herb Formulas with Illustrations, Oriental Healing Art Institute, California, (1980)). PHY906 consists of four herbs with proportion of *Scutellariae baicalensis Georgi* (scute), *Paeonia lactiflora pall* (white peony root), *Glycyrrhizae uralensis Fisch* (licorice) and the fruit of *Fructus ziziphi* (date) mixed in the proprotions1.5:1.0:1.0:1.0 by dry weight, respectively. It should be noted that each herb possesses a distinct pharmacological profile that includes anticancer and antiviral activity, hematological and immunological stimulation, analgesic activity, vasodilation, liver protection, antioxidation, and appetite improvement, as shown in Table 1.

TABLE 1. Putative Biological Activities of Individual Herbs in the PHY906 Formulation.

	Anti-Cancer	Immuno-Modulation	Anti-Bacteria	Anti-Inflammatory	Nervous System	Others
Scuellaria baicalensis Georgi	+	+ ↑↓ lymphocyte & macrophage activity bifunctional	+	+	-	antiviral, antibacterial antidiarrhea, diuretic, vasodilation,↓ lipid, anticoagulation, antioxidant, antiemetic, liver protection
Paeonia lactiflora pall	+	+ ↑↓ macrophage activity bifunctional modulator	+	+	+ analgesic	vasodilation, liver protection, diuretic anticoagulation, ↓ intestine movement
Fructus ziziphi	+	+ anti IgE action	-	-	+ ↑ sleep	liver protection, muscle endurance, improve appetite
Glycyrrhiza uralensis Fisch	+	+ ↑ macrophage activity ↑ interferon & ↑ IL-1 ↑ lymphocyte ↑ interferon & ↑ IL-2 ↑ NK activity ↓ IgE	+	+	+ analgesic	Antidiuretic ↓ intestine movement ↓ lipid (LDL, TC) antioxidant antiviral anticoagulation anticomplement

↑: increase ↓: decrease ↑↓: decrease or increase +: effect -: no effect

Until now, PHY906 has been prescribed as a single medicine only, rather than in combination with synthetic drugs. However, it is conceivable that one of the documented uses of PHY906 might actually be useful in alleviating the side effects induced by chemotherapy. Although some of the major chemical components in each of the four herbs of PHY906 have been identified, and their pharmacological activities have been examined (Chinese Botany Shanghai Science and Technology Publishing Company (1999); Huang, H-C, Wang, H-R, and Hsieh, L-M., Eur J of Pharmacol 251:91-93 (1994); Lin, C-C and Shieh, Am J Chinese Med 1:31-36 (1996); Tang, W. and Eisenbrand, G., Chinese Drugs of Plant Origin: Chemistry, Pharmacology and Use in Traditional and Modern Medicine pp. 919-929. Springer-Verlag Press, New York, (1992)), the biological properties of PHY906 may not be fully predicted by the identified ingredients.

SUMMARY OF THE INVENTION

The inventors of the present invention have unexpectedly discovered that the herbal composition PHY906 can be used in various methods for increasing the therapeutic index of one or more chemotherapeutic compounds and for modulating hematopoietic activity. The methods disclosed herein can be used to improve the quality of life for chemotherapy patients and to increase the dosage of chemotherapeutic agents because of the decreased toxicity of the agents when they are administered with PHY906.

This invention provides the herbal composition PHY906 combined with a pharmaceutically acceptable carrier and optionally including one or more chemotherapeutic compounds or antiviral agents. The four plant species which are chosen to make a particular formulation of PHY906 are each selected from one of four different groups of herbs: Scutellaria, Licorice, Peony Alba and Ziziphi Fruit. The herbs are chosen so as to obtain one or more of the desirable attributes of PHY906, wherein such attributes include, but are not limited to, increasing the therapeutic index of one or more chemotherapeutic compounds, enhancing the antitumor activity of one or more

chemotherapeutic compounds or enhancing the antiviral activity of one or more antiviral agents, modulating hematopoietic activity, modulating hematological and immunological activity, and improving the quality of life of a mammal undergoing chemotherapy or antiviral therapy.

Chemotherapeutic compounds or agents encompassed by this invention include, but are not limited to, those useful for treating cancer, parasitic infections, and microbial infections.

Antiviral compounds or agents encompassed by this invention include those that are useful for treating viral infections, diseases, or conditions.

The compositions and methods of the present invention are useful for treating any mammal. More specifically, the methods of the present invention are useful for treating humans.

This invention further provides compositions which include a pharmaceutically acceptable carrier; material or chemical from a plant species of each of the following genera of herbs: *Scutellaria*, *Glycyrrhiza*, *Ziziphus* and *Paeonia*; and one or more chemotherapeutic compounds. Preferably, the composition comprises a pharmaceutically acceptable carrier, an herbal preparation comprising *Scutellaria*, *Glycyrrhiza*, *Ziziphus* and *Paeonia,* and a chemotherapeutic formulation comprising one or more chemotherapeutic or antiviral agent. More preferably, the herbal preparation comprises material or chemical from *Scutellaria*, *Glycyrrhiza*, *Ziziphus* and *Paeonia*. Most preferably, this invention provides such compositions which include *Scutellaria baicalensis*, *Glycyrrhiza uralensis*, *Ziziphus jujuba*, and *Paeonia lactiflora*.

The herbal compositions of the present invention are particularly useful with cancer chemotherapies, such as, but not limited to, treatment with an irinotecan formulation (CPT-11, Camptosar®), 5-fluorouracil (FU or 5-FU), VP-16, beta-L-Dioxolane-cytidine (L-OddC), leucovorin (LV), and combinations thereof, such as but not limited to FU/LV and CPT-11/FU/LV.

The herbal compositions of the present invention are particularly useful with antiviral therapies. Preferably, the herbal compositions are administered with antiviral agents useful for treating AIDS. More preferably, the herbal compositions are administered with antiviral agents selected from the group consisting of AZT, D4T, and DDI.

The present invention provides methods for increasing the therapeutic index of cancer therapeutic compounds used in the treatment of cancer. The present invention also provides methods for increasing the therapeutic index of antiviral agents used in the treatment of antiviral diseases. More specifically, the present invention provides such methods which include administering one or more anticancer or antiviral agent in combination with a therapeutically effective amount of a composition comprising a pharmaceutically acceptable carrier and material or chemical from, or herbal preparation comprising a plant species of each of the following genera of herbs: *Scutellaria*, *Glycyrrhiza*, *Ziziphus* and *Paeonia*. The methods of the present invention provide the use of material or chemical from, or herbal preparation comprising such herbs which is in the form of a granulated extract from a concentrated aqueous liquor. Such compositions can be in an ingestible form, such as, but not limited to, powders, capsules, liquids and tablets. Alternatively, the methods of the present invention use such compositions in the form of a suppository.

The present invention also provides methods of treating diseases in mammals in need of such treatment which includes administering a therapeutically effective amount of a composition comprising a pharmaceutically acceptable carrier; material or chemical from, or herbal preparation comprising a plant species of each of the following genera of herbs: *Scutellaria*, *Glycyrrhiza*, *Ziziphus* and *Paeonia*; and one or more chemotherapeutic compounds.

The present invention further provides methods of treating diseases in a mammal in need of such treatment which includes administering a therapeutically effective amount of one or more chemotherapeutic compounds or antiviral agents and a composition which

includes a pharmaceutically acceptable carrier; material or chemical from, or herbal preparation comprising a plant species of each of the following genera of herbs: *Scutellaria*, *Glycyrrhiza*, *Ziziphus* and *Paeonia*. The present invention includes such methods wherein the composition is administered before the administration of the one or more chemotherapeutic compounds. The present invention also includes such methods wherein the composition is administered after the administration of the one or more chemotherapeutic compounds.

The present invention provides methods of modulating hematopoietic activity for the treatment of a disease by administering to a mammal in need of such treatment a therapeutically effective amount of a composition consisting essentially of a pharmaceutically acceptable carrier and material or chemical from or herbal preparation comprising a plant species of each of the following genera of herbs: *Scutellaria*, *Glycyrrhiza*, *Ziziphus* and *Paeonia*. The present invention provides such methods wherein the material or chemical from the herbs is in the form of a granulated extract from a concentrated aqueous liquor. Specifically, the present invention provides such methods wherein the composition is in an ingestible form, such as, but not limited to, powders, capsules, liquids and tablets. Alternatively, the present invention provides such methods wherein the composition is in the form of a suppository.

The present invention also provides methods of improving the quality of life of a mammal undergoing chemotherapy or antiviral therapy which comprises administering a therapeutically effective amount of one or more chemotherapeutic compounds and a composition comprising:

i) a pharmaceutically acceptable carrier;

ii) material or chemical from a plant species of each of the following genera of herbs: *Scutellaria*, *Glycyrrhiza*, *Ziziphus* and *Paeonia*.

The present invention contemplates administering a chemotherapeutic formulation comprising one or more chemotherapeutic agents in combination with a composition comprising a pharmaceutically acceptable carrier and an herbal preparation comprising a

plant species of each of the following genera of herbs: *Scutellaria*, *Glycyrrhiza*, *Ziziphus* and *Paeonia*.

The present invention also contemplates administering a antiviral formulation comprising one or more antiviral agents in combination with a composition comprising a pharmaceutically acceptable carrier and an herbal preparation comprising a plant species of each of the following genera of herbs: *Scutellaria*, *Glycyrrhiza*, *Ziziphus* and *Paeonia*.

The present invention uses the disclosed herbal compositions for increasing the antitumor activity of chemotherapeutic agents, increasing the antiviral activity of antiviral agents, decreasing the toxicity of the chemotherapeutic or antiviral agent, modulating the hematological and immunological activity of a mammal, and improving the quality of life of a mammal undergoing chemotherapy or antiviral therapy

In one aspect, the present invention discloses a method of treatment comprising a chemotherapeutic regimen comprising one or more chemotherapeutic compounds and a composition comprising a pharmaceutically acceptable carrier and an herbal preparation comprising *Scutellaria*, *Glycyrrhiza*, *Ziziphus* and *Paeonia*. In another aspect, the present invention discloses a method of treatment comprising an antiviral regimen comprising one or more antiviral agents and a composition comprising a pharmaceutically acceptable carrier and an herbal preparation comprising *Scutellaria*, *Glycyrrhiza*, *Ziziphus* and *Paeonia*.

Further, the present invention provides a therapeutic regimen comprising one or more chemotherapeutic or antiviral compound and a composition comprising a pharmaceutically acceptable carrier and an herbal preparation comprising *Scutellaria*, *Glycyrrhiza*, *Ziziphus* and *Paeonia*.

Additionally, the present invention discloses chemotherapeutic regimens and compositions comprising three chemotherapeutic compounds, preferably, CPT-11, FU, and LV and an herbal preparation comprising *Scutellaria*, *Glycyrrhiza*, *Ziziphus* and *Paeonia* or material or chemical from a plant species of each of the following genera of herbs *Scutellaria*, *Glycyrrhiza*, *Ziziphus* and *Paeonia*. The present invention

contemplates antiviral therapies comprising one or more antiviral agents.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1. Effect on Different Dosage of CPT-11 in Non-tumor Bearing BDF-1 Mice. CPT-11 was given intraperitoneally (i.p.) on day 0 only (N=5 in each group).

Figure 2. Effect of PHY906 on Body Weight in CPT-11 Treated BDF-1 Mice Bearing Colon 38 Tumor. CPT-11 (400 mg/kg) was given intraperitoneally on day 0 only. PHY906 was given orally twice a day for 8 days beginning on day 0 at the dose indicated (N=5 in each group).

Figure 3. Effect of PHY906 on Tumor Growth in CPT-11 Treated BDF-1 Mice Bearing Colon 38 Tumor. CPT-11 (400 mg/kg) was given intraperitoneally on day 0 only. PHY906 (500 mg/kg) was given orally twice a day for 8 days beginning on day 0. The p values were calculated using the Student's paired t-test.

Figure 4. Effect of PHY906 on Hematological Change in CPT-11 Treated BDF-1 Mice Bearing Colon 38 Tumor (N=5 in each group). CPT-11 (400 mg/kg) was given intraperitoneally on day 0 only. PHY906 (500 mg/kg) was given orally twice a day for 4 days beginning on day 0 (N=5 in each group).

Figure 5. Effect of PHY906 on Body Weight in FU/LV Treated BDF-1 Mice Bearing Colon 38 Tumor. Sequential administration of LV (100 mg/kg) and FU (100 mg/kg) was given intraperitoneally during 1 hr period on day 0 only, as described in Materials and Methods. PHY906 was given orally 30 min after initial dose of LV on day 0 and continued twice a day for 4 days at 500 mg/kg (N=5 in each group).

Figure 6. Effect of PHY906 on Tumor Growth in FU/LV Treated BDF-1 Mice

Bearing Colon 38 Tumor. Sequential administration of LV (100 mg/kg) and FU (100 mg/kg) was given intraperitoneally during 1 hr period on day 0 only, as described in Materials and Methods. PHY906 was given orally 30 min after initial dose of LV on day 0 and continued twice a day for 4 days at 500 mg/kg (N=5 in each group).

Figure 7. Effect of PHY906 on Hematological Change in FU/LV Treated BDF-1 Mice Bearing Colon 38 Tumor. Sequential administration of LV (100 mg/kg) and FU (100 mg/kg) was given intraperitoneally during 1 hr period on day 0 only, as described in Materials and Methods. PHY906 was given orally 30 min after initial dose of LV on day 0 and continued twice a day for 4 days at 500 mg/kg (N=5 in each group).

Figure 8. Effect of PHY906 on Tumor Growth in CPT-11/FU/LV Treated BDF-1 Mice Bearing Colon 38 Tumor. Sequential administration of LV (100 mg/kg), CPT-11 (200 mg/kg) and FU (100 mg/kg) was given intraperitoneally during 1 hr period on day 0 only, as described in Materials and Methods. PHY906 was given orally 30 min after initial dose of LV on day 0 and continued twice a day for 4 days at 500 mg/kg (N=5 in each group).

Figure 9. Effect of PHY906 on Tumor Growth in CPT-11/FU/LV Treated BDF-1 Mice Bearing Colon 38 Tumor. Sequential administration of LV (100 mg/kg), CPT-11 (300 mg/kg) and FU (100 mg/kg) was given intraperitoneally during 1 hr period on day 0 only, as described in Materials and Methods. PHY906 was given orally 30 min after initial dose of LV on day 0 and continued twice a day for 4 days at 500 mg/kg (N=5 in each group).

Figure 10. Effect of PHY906 on Body Weight Change in CPT-11/FU/LV Treated BDF-1 Mice Bearing Colon 38 Tumor. Sequential administration of LV (100 mg/kg), CPT-11 (300 mg/kg) and FU (100 mg/kg) was given intraperitoneally during 1 hr

period on day 0 only, as described in Materials and Methods. PHY906 was given orally 30 min after initial dose of LV on day 0 and continued twice a day for 4 days at 500 mg/kg (N=5 in each group).

Figure 11. Effect of PHY906 on the Tumor Growth in CPT-11 Treated NCr-Nude Mice Bearing Human HepG2 Tumor. CPT-11 (200 mg/kg) was given intraperitoneally on day 0 only. PHY906 was given orally 30 min before CPT-11 on day 0 and continued twice a day for 8 days at 500 mg/kg (N=5 in each group).

Figure 12. Effect of PHY906 on the Body Weight in CPT-11 Treated NCr-Nude Mice Bearing Human HepG2 Tumor. CPT-11 (200 mg/kg) was given intraperitoneally on day 0 only. PHY906 was given orally 30 min before CPT-11 on day 0 and continued twice a day for 8 days at 500 mg/kg (N=5 in each group).

Figure 13. Antitumor Effect of L-OddC with PHY906 on Colon 38 Bearing BDF-1 Mice. Five female BDF-1 mice (8-10 weeks old, average weight about 20g) were injected subcutaneously with Colon 38 tumor cells. Only one dose of L-OddC (beta-L-Dioxolane-cytidine 25 mg/kg, q.d.X5) was injected intraperitoneally on day zero. PHY906 was administered orally (1 g/kg, b.i.d.) on day zero and on a daily basis until the completion of the experiment (q.d. is an abreviation for "quaque die" which means once a day, q.d. X5 means each one of five mice received the dose once a day; b.i.d. is an abbreviation for "bis in die", which means twice a day). Tumor weight was calculated as described under Materials and Methods.

Figure 14. Antitumor Effect of VP-16 with PHY906 on Colon 38 Bearing BDF-1 Mice. Five female BDF-1 mice (8-10 weeks old, average weight about 20g) were injected subcutaneously with Colon 38 tumor cells. Only one dose of VP-16 (etoposide 25 mg/kg, q.d.X5) was injected intraperitoneally on day 0. PHY906 was administered

orally (1 g/kg, b.i.d.) on day 0 and on a daily basis until the completion of the experiment. Tumor weight was calculated as described under Materials and Methods.

Figure 15. Antitumor Effect of 5-Fluorouracil (FU) with PHY906. Five female BDF-1 mice (8-10 weeks old, average weight about 20g) were injected subcutaneously with Colon 38 tumor cells. Only one dose of FU (250 mg/kg) was injected intraperitoneally on day zero. PHY906 was administered orally (1 g/kg, b.i.d.) on day zero and on a daily basis until the completion of the experiment. Tumor weight was calculated as described under Materials and Methods.

Figure 16. Antitumor Effect of 5-Fluorouracil (FU) with PHY906. Five female BDF-1 mice (8-10 weeks old, average weight about 20g) were injected subcutaneously with Colon 38 tumor cells. FU (30 mg/kg, q.d. X 5) was injected intraperitoneally daily. PHY906 was administered orally (1 g/kg, b.i.d.) on day 0 and on a daily basis until the completion of the experiment. Tumor weight was calculated as described under Materials and Methods.

Figure 17. Antitumor Effect of CPT-11 with PHY906 Versus Loperamide on Colon 38 Bearing BDF-1 Mice. Five female BDF-1 mice (8-10 weeks old, average weight about 20g) were injected subcutaneously with Colon 38 tumor cells. Mice either received no treatment, PHY906 alone, CPT-11 alone, CPT-11 and PHY906, or Loperamide alone. The PHY906 and CPT-11 were administered as set forth in Figure 3. Only one dose of Loperamide was injected peritoneally (2 mg/kg, p.o. (oral administration), b.i.d.)on day zero. Tumor weight was calculated as described under Materials and Methods.

Figures 18A-C. Pharmacokinetic of CPT-11/FU/LV in Plasma. PHY906-6 is the clinical batch of PHY906. SN-38 is an active metabolite of CPT-11. FUR+FUMP are nucleoside and nucleotide metabolites of FU.

Figures 19A-C. Pharmacokinetic of CPT-11/FU/LV in Liver. PHY906-6 is the clinical batch of PHY906. SN-38 is an active metabolite of CPT-11. FUR+FUMP are nucleoside and nucleotide metabolites of FU.

Figures 20A-B. Pharmacokinetic of CPT-11/FU/LV in Tumor. PHY906-6 is the clinical batch of PHY906. SN-38 is an active metabolite of CPT-11.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Cancer chemotherapeutic agents often induce severe adverse side effects that can affect patients' quality-of-life, as well as interfere with the therapeutic regimen. The present invention is based in part on the discovery that Chinese herbal medicines in combination with standard anticancer agents is useful for reducing the adverse side effects of cancer chemotherapeutic agents and for improving the quality of life of patients undergoing chemotherapy. PHY906, a botanical formulation composed of four distinct herbs, has been used for centuries for the treatment of various gastrointestinal ailments and other illnesses in China. The present invention is based on the results of experiments performed in animal models evaluating the potential efficacy of PHY906 in relieving side effects induced by cancer chemotherapy agents in colorectal cancer patients. Specifically, the present invention is based in part on the finding that PHY906 reduces various host toxicity induced by CPT-11, FU, FU/LV, CPT-11/FU/LV, L-OddC, VP-16, or CPT-11/loperamide treatment, as well as maintaining and even potentiating the antitumor activity of chemotherapeutic agents. More specifically, PHY906 enhances the therapeutic index of CPT-11, and a triple combination of CPT-11/FU/LV by both potentiating antitumor effects of the therapeutic agents and reducing various host toxicities. These

findings are not limited to one specific anticancer agent or one specific tumor model.

The present invention is also based in part on the discovery of a regimen that can be used in conjunction with various anticancer agents to lower the dose limiting toxicity and increase efficacy of the agents. This discovery is an extremely important addition to the armamentarium of treatment approaches for human cancers.

I. Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are described.

As used herein, "cancer chemotherapeutic" or "cancer chemotherapeutic agent" refers to chemotherapeutic agent for the treatment of neoplastic disease or cancer.

As used herein, "chemotherapy" refers to treatment of disease by means of chemical substances or drugs.

As used herein, the term "chemotherapeutic formulation" refers to a composition comprising a chemotherapeutic agent.

As used herein, the term "extract" refers to a concentrated preparation of a vegetable or animal drug obtained by removing the active constituents therefrom with a suitable menstruum (solvent), evaporating all or nearly all the solvent and adjusting the residual mass or powder to a prescribed standard. Extracts are prepared in three forms, semiliquid or of syrupy consistency, pilular or solid, and as dry powder (see http://www.graylab.ac.uk/cgi-bin/omd?query=extract).

In one embodiment, extracts are concentrated forms of crude drugs used in a variety of solid and semisolid dosage forms (in Remington's Pharmaceutical Sciences 17th ed. (*Gennaro*, ed), Chapter 84, pp. 1516-1517, Mack Publishing Co, Easton, PA

(1985)). For example, pilular (*i.e.*, plastic masses) extracts are of a consistency where they are suitable for pill masses and are made into pills (*e.g.*, pure *Glycyrrhiza* extract USP). Further, pilular masses are well suited for use in ointments and suppositories. Powdered extracts are better suited for powdered formulations such as capsules, powders and tablets. Further, semiliquid or extracts of syrupy consistency can be used in the manufacture of pharmaceutical preparations (Remington's Pharmaceutical Sciences, 1985).

In a related aspect, extracts can be considered solutions of active ingredients obtained by soaking or steeping preparations of vegetable or animal crude drugs in liquids (maceration) or by passing such crude drugs through porous substances (percolation) for use as a medicinal agent. Further, medicinal agents of this type may be in the form of tinctures or fluidextracts [sic] (Remington's Pharmaceutical Sciences, 1985).

In one embodiment, the extract is in tincture form. For example, tinctures may include, but are not limited to, alcoholic or hydroalcoholic solutions prepared from vegetable matter or from chemical substances. Tinctures may be made by either percolation or maceration and are traditionally assigned potency by the amount of activity of a specified weight of the drug (in grams) per 100 ml of tincture (Remington's Pharmaceutical Sciences, 1985). For example, Sweet Orange Peel Tincture contains 50 g of sweet orange peel per 100 ml of tincture.

In another embodiment, the extract is in fluidextract [sic] form. For example, fluid extracts include, but are not limited to, liquid preparations of vegetable drugs comprising alcohol as the solvent or as a preservative, or both, where traditionally each ml contains the therapeutic constituents of 1 gram of the drug that it represents. Fluidextracts can be made by percolation as a general method (Remington's Pharmaceutical Sciences, 1985).

As used herein, the term "hematological activity" refers to activity associated with blood and blood forming organs.

Technically speaking, the term "herb" refers to a small, non-woody (*i.e.*, fleshy stemmed), annual or perennial seed-bearing plant in which all the aerial parts die back at the end of each growing season. Herbs are valued for their medicinal, savory or aromatic qualities. As the word is more generally used and as the word is used herein, an "herb" refers to any plant or plant part which has a food supplement, medicinal, drug, therapeutic, or life-enhancing use. Thus, as used herein, an herb is not limited to the botanical definition of an herb but rather to any botanical, plant or plant part used for such purposes, including any plant or plant part of any plant species or subspecies of the Metaphyta kingdom, including herbs, shrubs, subshrubs, and trees. Plant parts used in herbal compositions include, but are not limited to, seeds, leaves, stems, twigs, branches, buds, flowers, bulbs, corns, tubers, rhizomes, runners, roots, fruits, cones, berries, cambium and bark.

As used herein, an "herbal composition or formulation" refers to any composition or formulation which includes herbs, herbal plants, herbal plant parts and/or herbal extracts. Thus, as used herein, an herbal composition or formulation includes herbal preparation comprising herbal food supplements, herbal medicines, herbal drugs, and medical foods. Examples of herbal compositions include, but are not limited to, the following components: a whole plant or a plant part of a single plant species; whole plants or plant parts of multiple plant species; multiple components derived from a single plant species; multiple components derived from multiple plant species; herbal extracts; or any combination of these various components. Also contemplated are herbal compositions comprising one or more chemicals derived from a single or multiple plant species.

For a thorough review of various herbal compositions, see, for example, Kee Chang Huang, The Pharmacology of Chinese Herbs, CRC Press (1993), herein incorporated in its entirety.

As used herein, the term "immunological activity" refers to activity associated with the immune system, immunity, induced sensitivity, and allergy.

As used herein, the term "mortality rate" refers to the proportion of deaths in a population or to a specific number of the population, where mortality is defined as the death rate or ratio of the total number of deaths to the total population. For example, the 30 day mortality rate after ischemic stroke symptom onset can vary from about 13.3% (*e.g.*, after treatment with tissue type plasminogen activator, see Albers *et al., JAMA* (2000) 283(9):1145-1150) to greater than about 65% (*e.g.*, hemorrhage stroke, see Mahaffey *et al., Am Heart J* (1999) 138(3 Pt 1):493-499).

As used herein, the term "Quality of life (QOL)" refers to the general well-being of an animal, especially a mammal, even more specifically a human. The QOL of an individual can be evaluated based on any one parameter, a group of two or more parameters or on a general overall evaluation or score. Examples of useful indices for evaluating QOL include, but are not limited to, those associated with sleeping patterns; eating patterns; drinking patterns; agility; mobility; skin tone; vision; hair retention/loss/growth; muscle tone; muscle mass; strength; weight; sinus health; presence, absence or degree of inflammation; feelings of discomfort; ability to accomplish specific tasks; anxiety levels; response times; ability to concentrate; memory retention; verbal ability; sound perception; presence, absence or degree of headaches; muscle spasms; nerve damage; taste; touch; smell; presence or absence of opportunistic diseases; and presence or absence of parasites.

As used herein, the term "regimen" refers to a program of treatment.

As used herein, the term "therapeutic index" refers to how selective a drug is in producing the desired effects. Therapeutic index is the ratio of LD_{50} to ED_{50}. ED_{50}, the median effective dose, is the dose of a drug required to produce a specified effect in 50% of the population. LD_{50} is the median lethal dose as determined in experimental animals.

II. Specific Embodiments

A. Chemotherapy.

In general, chemotherapy refers to the treatment of disease, especially neoplasms, parasitic infections and microbial diseases, with chemical agents that in some manner act on the infective organisms or tumors.

1. Cancer Chemotherapy

Introduction: Chemotherapy continues to be one of the most effective modalities for treating cancer in patients. Although quite effective, chemotherapeutic agents are also well known to adversely disrupt the quality-of-life of patients. Some commonly observed side effects include myelosuppression and immunosuppression, diarrhea, peripheral neuropathy, nausea and vomiting, fever, liver dysfunction and cardiac toxicity, *etc.* (" Physicians Desk Reference" (1999) Medical Economics Company). In many instances, these adverse side effects prevents patients from receiving escalating doses or additional courses of therapy, thereby comprising the efficacy of these agents. Alleviation of some or all of these side effects, without compromising the anticancer activity of chemotherapeutic agents, would not only improve the quality-of-life (QOL) of cancer patients, but also allow for a more aggressive treatment protocol, resulting in possibly improved clinical success. Currently, most supportive therapies use single agents, such as anti-emetics, anti-mucositis agents, and colony growth factors, that target individual side effects, but do not address the broad spectrum of side effects associated with cancer chemotherapy (Bleiberg H and Cvitkovic E., Eur J Cancer 32A(Suppl 3):S18-S23 (1996); Wierda D. and Matamoros M., Toxicol & Applied Pharmacol 75:25-34(1984); Goldber R.M. and Erlichman C., Oncology 12: 59-63 (1988)).

Drugs for treating cancer include the more conventional natural products such as paclitaxel (TAXOL), the semisynthetics such as etoposide, and many newer, diverse agents such as interleukin-2 and all-trans-retinoic acid. For a comprehensive list of

chemotherapeutic agents useful in treating neoplastic diseases, see, for example, Table X-1 at pages 1227-1229 of Calabresi and Chabner (1996).

The major adverse effects associated with commonly administered cancer chemotherapies are provided in Table 2.

Table 2. Major Adverse Effects of Cancer Chemotherapy.

Major Adverse Health Effects	Antineoplastic Agent
Pancreatitis	VP-16, ara C
Alopecia	VP-16, Doxorubicin, Taxol, FU, araC
Cardiotoxicity	Taxol, Doxorubicin
Cutaneous	Doxorubicin
Diarrhea	CPT-11
Dyspnea	ara C
Flush	Tamoxifen
Fever/Chills	VP-16, Doxorubicin
Hepatotoxicity	VP, Taxol, ara C, Methotrexate
Nephrotoxicity	Cisplatin
Ototoxicity	Cisplatin
Bone Marrow Hypoplasia	Almost all anticancer drugs

5-Fluorouracil: The fluoropyrimidine analog, 5-fluorouracil (5-FU or FU), exhibits a broad spectrum of clinical activity. It remains one of the most active agents in the treatment of colorectal cancer both in the adjuvant and advanced disease setting, and in other GI malignancies as well (Pinedo and Peters, 1988). In addition, this agent is active against cancers of the breast, and head and neck.

Recent advances in the therapy of colorectal cancer have used biochemical modulation to selectively activate specific pyrimidine metabolic pathways. The reduced folate, leucovorin (LV), is an effective biochemical modulator and has been used in clinical treatments in combination with FU (Peters and Van Groeningen, 1991; Joulia, *et al.*, 1999). It has been shown that the addition of exogenous folate in the form of LV enhances responses to FU in clinical trials (Calabresi and Chabner, Page 1250, 1996).

The purported mechanism of interaction of LV is enhanced thymidylate synthase inhibition.

The response rate to FU in patients with advanced disease is improved from 10% - 12% (FU treatment alone) to 20%-30% (FU/LV treatment).

For a detailed description of the therapeutic uses of the fluoropyrimidine analogs, including FU, see, for example, Chabner *et al.*, 1996.

CPT-11: Irinotecan (CPT-11) is a semi-synthetic camptothecin analogue that inhibits topoisomerase I in the replicating cell. It exhibits anti-tumor activity in cancer patients who fail first-line treatment with FU/LV (Bleiberg, 1999; Stucky-Marshall, 1999).

While CPT-11 is FDA-approved as a second-line therapy for patients with advanced colorectal cancer, the observed response rates are on the order of only 10% - 15%.

The main side effects associated with this agent include leukopenia, anemia, nausea/vomiting, anorexia, and diarrhea. It is, therefore, desirable to develop a modulator agent that can either enhance the efficacy of the anti-tumor activity of CPT-11 and/or alleviate some of the toxic side effects associated with CPT-11 treatment so that the overall quality of life and performance status of the cancer patient is improved.

CPT-11/FU and CPT-11/FU/LV Combination: Colorectal cancer has been reported to be the second-leading cause of death from cancer in North America. The two drugs that are currently approved by the FDA for the treatment of colorectal cancer are irinotecan (CPT-11, Camptosar®) and 5-fluorouracil (FU). FU is an antimetabolite drug, which inhibits thymidylate synthase, an enzyme required for the synthesis of DNA. FU is commonly administered with LV, a reduced folate that increases the affinity of FU for thymidylate synthase, This therapy is currently used as first-line treatment for metastatic colon cancer (Murakami K, Sakukawa, R, Sano, M, *et al.*, Clin Cancer Res. 5:2304-2310